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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/285,531	04/02/1999	YUTI CHERNAJOVSKY	KIR95-01A	3818

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	28

DATE MAILED: 12/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/285,531	CHERNAJOVSKY ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,8,14-17 and 19-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *29 and 30* is/are allowed.

6)☒ Claim(s) *1-3,6,8,14-17,19-28 and 31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Claims

1. Claims 1-3, 6, 8, 14-17, 19-37 are pending in the instant application. Claims 20-23, 27 and 34-37 have been amended as requested by Applicant in Paper Number 25, filed March 19, 2003.

Claim Objections

2. Claim 14 is objected to because of the following informalities: It recites "Isolated DNA comprising a receptor molecule" and, and DNA does not comprise a protein. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. Claims 14, 28 and 31-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 28 are indefinite because they encompasses a DNA molecule encoding a protein comprising a polypeptide linker wherein in the linker is from about 10 to about 30 amino acid residues in length, but the claims also recite that the DNA comprises SEQ ID NO: 1 or the protein has the sequence of SEQ ID NO: 2, which is a defined nucleic acid sequence that encodes a specific protein having a defined linker sequence (15 amino acids). A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by

the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). Claims 32-37 are rejected for depending from claim 28.

Claim 31 is indefinite because it encompasses a method of making a construct to express the protein of SEQ ID NO: 2, which consists of two extracellular domains of tumor necrosis factor, but the method of dependent claim 31 is drawn to making a construct comprising three extracellular domains of tumor necrosis factor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4.1 Claims 1-3, 6, 8, 15-17 and 19-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallach et al., U.S. Patent No. 5,478,925 (Wallach I), or Wallach et al., EP 0 526 905 (Wallach II), in view of Paul et al., U.S. Patent No. 5,736,387, for reasons of record in

the previous Office Actions, Paper No. 26, Paper No. 20, Paper No. 18, and Paper No. 8, and below.

Claims drawn to the nucleic acid of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2 have been withdrawn from the rejections, because the references of record do not suggest the single claimed species with the particularity required to support a prima facie case of obviousness. *Compare In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

The teachings of Wallach et al. (I and II) were discussed in the previous office actions. Paul et al. teach chimeric proteins that comprise a flexible polypeptide linker sequence (flexon), that most preferably comprises between ten and thirty amino acids, which may be comprised of glycine residues (column 11, lines 5-42 and column 20, lines 34-54, Examples 6 and 7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a fusion protein comprising two or three human p55 and/or p75 TNFR extracellular domain sequences, joined by suitable linker sequences that are ten to thirty amino acids in length, as taught by Paul et al., and optionally comprising a signal sequence for production in an appropriate host cell, because Wallach teaches that it is advantageous to do so, and Paul et al. teaches that incorporating "flexons" between the different moieties of the fusion protein would promote functionality of the different moieties on the two sides of the flexon by allowing a moiety on one side of the flexon to adopt a conformation relatively independently from that of the moiety on the other side of the flexon.

Applicants traverse the rejections and assert that the claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has the potential to cause side effects, and that these features combined make this molecule

unexpectedly superior to known TNF receptor-based molecules. Applicants assert that the cited references fail to support a *prima facie* case of obviousness, since joining monomers covalently via a peptide linker is but only one method out of a veritable universe of possibilities taught by the references, and that the Examiner incorrectly relies on the teaching of Wallach I and II that "those of ordinary skill in the art will be able determine" the [linker] length for optimum activity. Applicants argue that at most, the possibility that one skilled in the art could have optimized a linker length using routine experimentation is merely an invitation to experiment further, and such a possibility, as taught by the art, does not constitute the teaching of the linker length, i.e., 10-30 residues, which applicants actually conceived. Applicants also assert that when combined with routine skill, Wallach I and II also fail to provide a reasonable expectation of success, and offer no experimental evidence demonstrating the success of their claimed multimers, and fail to provide guidance as to how one would arrive at a linker length which would provide the unexpected advantages seen with the instant molecule.

Applicants' arguments have been fully considered but are not deemed persuasive. Although Wallach I and II may teach a number of ways of joining TNF receptors to construct multimers, this does not negate the teaching of joining monomers covalently via a peptide linker. Wallach I and II may not offer experimental results, but they offer ample guidance to one of ordinary skill in the art to determine what an optimal linker length would be, and though some experimentation would be required, such experimentation would be routine. There would be a reasonable expectation of success, since chimeric proteins comprising linker sequences and having desired functional characteristics had been constructed at the time of the invention, and

Paul et al. teaches that optimal linker lengths of ten to thirty amino acids would allow moieties at either end of the linker to adopt a conformation relatively independently from each other.

4.2 Claims 1-3, 6, 8, 15-17 and 19-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. PN 5,395,760, March 7, 1995, view of Paul et al., U.S. Patent No. 5,736,387, for reasons of record in the previous Office Actions, Paper No. 26, Paper No. 20, Paper No. 18, and Paper No. 8, and below.

Claims drawn to the nucleic acid of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2 have been withdrawn from the rejections, because the references of record do not suggest the single claimed species with the particularity required to support a prima facie case of obviousness. *Compare In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

The teachings of Smith et al. were discussed in the previous office actions. The teachings of Paul et al. are described above. It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to make a dimeric or polyvalent TNF receptor molecule comprising the extracellular domains of TNF-R as suggested by Smith et al., joined by suitable linker sequences that are ten to thirty amino acids in length, as taught by Paul et al. One of ordinary skill in the art would have been motivated to do so, because of the number of different diseases found to be associated with TNF, and Paul et al. teaches that incorporating "flexons" between the different moieties of the fusion protein would promote functionality of the different moieties on the two sides of the flexon by allowing a moiety on one side of the flexon to adopt a conformation relatively independently from that of the moiety on the other side of the flexon, and Paul et al. also teach the preferred linker length to be between ten and thirty amino acids. There would have been a reasonable expectation of success, since production of chimeric

proteins was routine in the art at the time of the invention, and since TNF-R Ig fusions proteins were known to be effective for treatment.

Applicants traverse the rejection and assert that Smith et al. do not define the optimal length of this linker region, and Smith et al. suffers from the same deficiency seen in Wallach I and II, i.e., they teach a receptor-based molecule with a virtually infinite number of linker permutations, and the reference, in combination with routine skill, fails to teach or suggest all elements of the rejected claims, and fails to provide a reasonable expectation of success.

Applicants' arguments have been fully considered but are not deemed persuasive, for reasons given above under the rejection under Wallach I and II. Though some experimentation would be required, such experimentation would be routine. There would be a reasonable expectation of success, since chimeric proteins comprising linker sequences and having desired functional characteristics had been constructed at the time of the invention.

It is believed that all pertinent arguments have been answered.

Conclusion

5.1 Claims 29 and 30 are allowed.

5.2 1-3, 6, 8, 14-17, 19-28 and 31-37 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

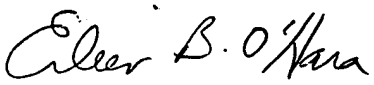
Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.



Patent Examiner